Chronic obstructive pulmonary disease: An independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease

AUTHOR(S):

Nishiyama, Kei; Morimoto, Takeshi; Furukawa, Yutaka; Nakagawa, Yoshihisa; Ehara, Natsuhiko; Taniguchi, Ryouji; Ozasa, Neiko; ... Fukushima, Masanori; Kita, Toru; Kimura, Takeshi

CITATION:

Nishiyama, Kei ...[et al]. Chronic obstructive pulmonary disease: An independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease. International journal of cardiology 2010, 143(2): 178-183

ISSUE DATE:

2010-08-20

URL:

http://hdl.handle.net/2433/128954

Elsevier Editorial System(tm) for International Journal of Cardiology
Manuscript Draft

Manuscript Number:

Title: Chronic Obstructive Pulmonary Disease—an Independent Risk Factor for Long-term Cardiac and Cardiovascular Mortality in Patients with Ischemic Heart Disease

Article Type: Original Article

Keywords: Chronic obstructive pulmonary disease, Ischemic heart disease, prognosis, Cardiac death, Cardiovascular death

Corresponding Author: Dr Kei Nishiyama,

Corresponding Author's Institution: Kyoto University Graduate School of Medicine

First Author: Kei Nishiyama

Order of Authors: Kei Nishiyama; Takeshi Morimoto, MD PhD; Satoshi Shizuta, MD ; Takahiro Doi, MD; Toru Kita, MD PhD; Takeshi Kimura, MD PhD

Manuscript Region of Origin: JAPAN

Abstract: Background:
Limited data are available on long-term mortality and morbidity of patients with chronic obstructive pulmonary disease (COPD) and ischemic heart disease. We examined how COPD affects the long-term mortality and morbidity after undergoing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).
Methods:
We analyzed 9877 consecutive patients who underwent their first elective PCI (n = 6878) and CABG (n = 2999) in 2000-2002 at 30 institutions listed in the CREDO-Kyoto registry.
Results:

COPD was diagnosed in 240 patients (2.4%). In-hospital mortality (1.3% vs. 1.2%, p = 0.972) did not differ between patients with and without COPD. During long-term follow up (42.8 months), 906 patients (9.4%) died, 517 (5.3%) of whom died of cardiovascular death and 376 (3.9%), of cardiac death. At 3 years, the unadjusted survival rate and the rates of freedom from cardiovascular death and cardiac death were 92.1%, 95.3%, and 96.5% in the total population and 82.8%, 91.7%, and 92.1% in patients with COPD respectively. Log-rank test indicated that COPD was associated with higher incidence of all-cause mortality (p < 0.0001), cardiovascular death (p = 0.0002), and cardiac death (p < 0.0001). Multivariate analyses indicated that COPD was an independent predictor of all-cause mortality (hazard ratio 1.36, p = 0.0003), cardiovascular death (hazard ratio 1.28, p = 0.0407), and cardiac death (hazard ratio 1.48, p = 0.003).
Conclusions:
COPD is an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease.

Suggested Reviewers:

Chronic Obstructive Pulmonary Disease—an Independent Risk Factor for Long-term Cardiac and Cardiovascular Mortality in Patients with Ischemic Heart Disease

Kei Nishiyama[a], M.D.

Takeshi Morimoto[b], M.D., PhD.

Satoshi Shizuta[a], M.D.

Takahiro Doi[a], M.D.

Toru Kita[a], M.D., PhD.

Takeshi Kimura[a], M.D., PhD.

[a]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine

[b]Integrated Clinical Education Center, Kyoto University Hospital

Word count: 3641

Key words:

Chronic obstructive pulmonary disease, Ischemic heart disease, prognosis, Cardiac death, Cardiovascular death

All authors have read and approved the manuscript. No conflicts of interest exist among any of the authors in this study.

Address for correspondence:

Kei Nishiyama

Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine

54 Kawaharamachi, Shogoin, sakyo-ku, Kyoto 606-8397, Japan

TEL: 81-7-5751-3198, FAX: 81-7-5751-3299

E-mail: keinishi@kuhp.kyoto-u.ac.jp

Structured abstract (Word count = 248)

Background:

Limited data are available on long-term mortality and morbidity of patients with chronic obstructive pulmonary disease (COPD) and ischemic heart disease. We examined how COPD affects the long-term mortality and morbidity after undergoing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

Methods:

We analyzed 9877 consecutive patients who underwent their first elective PCI (n = 6878) and CABG (n = 2999) in 2000–2002 at 30 institutions listed in the CREDO-Kyoto registry.

Results:

COPD was diagnosed in 240 patients (2.4%). In-hospital mortality (1.3% vs. 1.2%, p = 0.972) did not differ between patients with and without COPD. During long-term follow up (42.8 months), 906 patients (9.4%) died, 517 (5.3%) of whom died of cardiovascular death and 376 (3.9%), of cardiac death. At 3 years, the unadjusted survival rate and the rates of freedom from cardiovascular death and cardiac death were 92.1%, 95.3%, and 96.5% in the total population and 82.8%, 91.7%, and 92.1% in patients with COPD respectively. Log-rank test indicated that COPD was associated with higher incidence of

all-cause mortality ($p < 0.0001$), cardiovascular death ($p = 0.0002$), and cardiac death ($p < 0.0001$). Multivariate analyses indicated that COPD was an independent predictor of all-cause mortality (hazard ratio 1.36, $p = 0.0003$), cardiovascular death (hazard ratio 1.28, $p = 0.0407$), and cardiac death (hazard ratio 1.48, $p = 0.003$).

Conclusions:

COPD is an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease.

Body of paper

Introduction

Chronic obstructive pulmonary disease (COPD) is a common comorbidity among patients undergoing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) [1-3]. Although some cohort studies have revealed that patients with COPD have a significantly higher risk of in-hospital mortality and long-term all-cause mortality following PCI and CABG [4-14], the effects of COPD on long-term mortality and morbidity in patients with ischemic heart disease have not been adequately demonstrated. To examine these effects, we evaluated the long-term outcomes of patients undergoing coronary revascularization in a large-scale multicenter registry in Japan.

Materials and methods

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) registry has collected data on the potential risk factors and outcomes in 9877 consecutive patients who underwent their first elective PCI (n = 6878) and CABG (n = 2999) at the 30 institutions between 2000 and 2002 in Japan. Patients with acute myocardial infarction within 1 week prior to the index procedure were excluded. The relevant review boards or ethics committees in all 30 participating centers (Appendix A) approved the research protocol. A description of the design and study protocol has been previously published[15] and the study protocol is concordant with the guidelines for epidemiologic studies issued by the Ministry of Health, Labor and Welfare of Japan. In order to examine whether COPD is an independent predictor of all-cause mortality, cardiovascular death, and cardiac death following PCI and CABG, we performed post hoc analysis of the data collected from 9756 consecutive patients who survived their first elective PCI (n = 6846) and CABG (n = 2910). The primary end point was all-cause mortality, cardiovascular death, and cardiac death. Demographic and angiographic characteristics before coronary intervention, and procedural data were collected from hospital charts or databases in each center by independent clinical research coordinators (Appendix B) according to prespecified definitions. Data in this

registry include patient demographics (e.g., age and gender), potential risk factors, and comorbidities (e.g., COPD, stroke, hypertension, and current smoking status) that have been demonstrated to be related to short-term and long-term outcomes.

All procedural decisions, including the technique of revascularization and device selection, were made at the discretion of the patient, the physician, and the surgeon performing PCI and CABG.

Definition

A patient was considered to have COPD if it was listed as a comorbid condition in our database and its diagnosis was confirmed by a simple test called spirometry, which measures how deeply a person can breathe and how fast air can move into and out of his or her lungs. Such a diagnosis should be considered in any patient who has symptoms of cough, sputum production, or dyspnea (difficult or labored breathing), and/or a history of exposure to risk factors for the disease. In cases where spirometry is unavailable, the diagnosis of COPD should be made using all available tools. Clinical symptoms and signs such as abnormal shortness of breath and increased forced expiratory time can be used to arrive at the diagnosis. A low peak flow is consistent with but not specific to COPD because it can be caused by other lung diseases and by poor

performance during testing. Chronic cough and sputum production often precede the development of airflow limitation by many years, although not all individuals with cough and sputum production go on to develop COPD. Congestive heart failure was diagnosed on the basis of clinical signs (New York Heart Association [NYHA] ≥ II). Diabetes or hypertension was considered to be present if the patients were previously diagnosed by another physician or if they were being treated with either insulin or oral antidiabetic drugs, or antihypertensive drugs respectively. Patients were considered to have a history of myocardial infarction if previously diagnosed by electrocardiogram or coronary angiography. The criteria for the diagnosis of periprocedural myocardial infarction were the appearance of new Q waves and an increase in creatine kinase to ≥2.0 times the upper limit of normal occurring ≤24 hours after PCI. Stroke at the baseline included asymptomatic stroke detected by non-invasive imaging modalities. Peripheral vascular disease was considered to be present when patients were being treated for carotid, aortic, and/or other peripheral vascular diseases or were scheduled for surgical or endovascular interventions. Left ventricular ejection fraction was measured either by contrast left ventriculography or echocardiography. Patients with left ventricular ejection fraction ≤ 40% were deemed to have left ventricular dysfunction. Chronic renal disease was identified when the creatinine clearance estimated by

Cockroft-Gault formula was less than 60 mL/min. Anemia was defined as blood hemoglobin level < 12 g/dL.

Long-term follow up was performed using outpatient visits and chart review. A central adjudication committee reviewed all deaths in a blinded fashion by using source documentation provided by the site investigators.

Statistical analysis

Standard descriptive statistics (proportions and 2 tests) were used to list patient and disease characteristics by subgroup. Statistical analysis of categorical variables was carried out using cross tables with the Pearson χ^2 test. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank statistics. To determine the baseline risk factors for the incidence of all-cause mortality, cardiovascular death, and cardiac death, we developed Cox proportional hazards models for the following 24 potential variables: COPD, the technique of revascularization, gender, body mass index, emergency procedure, prior myocardial infarction, congestive heart failure, stroke, peripheral artery disease, chronic atrial fibrillation, malignancy, hypertension, diabetes without insulin therapy, diabetes with insulin therapy, dialysis, chronic renal disease, anemia, current smoking status, left ventricular dysfunction, chronic total occlusion of

the coronary artery, proximal left anterior descending coronary artery disease, left main coronary artery disease, age, and triple vessel disease. All continuous variables were dichotomized so as to agree with the proportional assumptions according to the predetermined clinical contexts. We plotted log (time) vs. log[–log (survival)] stratified by each significant risk factor and evaluated whether the plotted lines were parallel[16]. The variables for which p values were less than 0.05 in univariate analyses and proportional assumptions were generally fair were included in the multivariate analyses. We developed multivariate Cox proportional hazards models that controlled for significant risk factors while testing for significant differences in long-term results. The appropriateness of the proportional hazards assumption for these variables has been attested elsewhere (Kimura manuscript). All analyses were performed with JUMP version 6.0.3 (SAS; Cary, NC).

Results

COPD was diagnosed in 240 patients (2.4%) on the basis of the baseline characteristics, which are shown in Table 1. Patients with COPD were more likely to have congestive heart failure, stroke, peripheral artery disease, chronic renal disease, anemia, and left ventricular dysfunction. They also tended to be older and had a lower average body mass index. Patients without COPD were more likely to be women and having diabetes that did not require insulin therapy. No difference was detected in the current smoking status in the 2 groups.

In-hospital mortality (1.3% vs. 1.2%, p = 0.9724) and in-hospital Q-wave myocardial infarction incidence (0.8% vs. 0.9%, p = 0.8572) did not differ between the groups (Table 2).

A total of 98% and 95% patients continued to attend follow-up examinations at the end of 1 and 2 years respectively. During long-term follow up (median follow-up period = 42.8 months), 906 patients (9.4%) died, 517 (5.3%) of which died of cardiovascular death and 376 (3.9%), of cardiac death. Of the total population, 265 patients (2.7%) suffered acute myocardial infarction, and 468 (4.8%) suffered stroke. Of the patients with COPD, 50 (21.3%) died, of which 24 (10.3%) died of cardiovascular death, and 22 (9.4%), of cardiac death. A total of 6 COPD patients (2.6%) suffered acute

myocardial infarction, and 11 (4.7%) suffered stroke. At 3 years, the unadjusted survival rate and the rates of freedom from cardiovascular death and cardiac death were 92.1%, 95.3%, and 96.5% in the total population and 82.8%, 91.7%, and 92.1% in patients with COPD, respectively.

Univarate analysis revealed that COPD was associated with higher all-cause mortality ($p < 0.0001$), cardiovascular death ($p = 0.0002$), and cardiac death ($p < 0.0001$); Kaplan-Meier survival curves are presented in Figure 1.

Multivariate analyses (considering the baseline characteristics and the results of univariate analyses) indicated that COPD was an independent predictor of all-cause mortality, cardiovascular death, and cardiac death after PCI and CABG (Table 3).

Discussion

Smoking as a risk factor is common to both COPD and ischemic heart disease; hence, these 2 diseases often coexist [17, 18]. Previous studies have shown that patients with COPD have a significantly higher risk of long-term all-cause mortality after PCI and CABG [5-14]. The manner in which COPD affects long-term mortality and morbidity in patients with ischemic heart disease remains unresolved. We analyzed 9877 consecutive patients who underwent their first elective PCI (n = 6878) and CABG (n = 2999) at 30 institutions in Japan. Univariate and multivariate analyses in this study indicated that COPD was an independent predictor of all-cause mortality. To our knowledge, this study is the first to show that patients with COPD have a significantly higher risk of cardiac and cardiovascular death following PCI and CABG.

The manner in which COPD affects the incidence of long-term adverse cardiac events after coronary revascularization is not quite clear. It was reported that patients affected by COPD have an increased risk of acute atherothrombotic events, and that this increase is independent of smoking and other cardiovascular risk factors. Further, bronchial inflammation reportedly spreads to the systemic circulation and is known to play a key role in plaque formation and rupture [19]. While the current smoking status did not differ between patients with and without COPD, this study reported that patients

with COPD were more likely to have peripheral artery disease and stroke as pre-operative comorbidities. Exacerbation of COPD may overtax an already diseased heart because of hypoxemia and increased work of breathing. It was reported that severe hypoxemia can worsen cardiac ischemia in patients with ischemic heart disease [20, 21]. On the other hand, exacerbation of ischemic heart disease can further impair gas exchange by incrementally increasing airway resistance or reducing mixed venous oxyhemoglobin saturation. Cardiac arrhythmias are frequent among patients with COPD. Previous studies reported widely various incidence of arrhythmia and arrhythmia related death in patients with COPD and it was reported that about ten percent of patients with COPD suffer from SCD[22-26]. However, the role of serious ventricular arrhythmias in these situations is unknown[27]. An association between severe COPD and increased QTc dispersion was reported, which has been reported as a marker of ventricular electrical instability[28]. It is not clear whether treating asymptomatic ventricular arrhythmia can reduce the incidence of SCD or not in patients with COPD[22-26] . This study demonstrated that COPD was associated with a higher incidence of long-term cardiac and cardiovascular mortality and morbidity. However additional interventional therapy for COPD was not recorded in our database, and so further study may be needed to investigate l whether intervention for COPD can improve long-term

mortality and morbidity from cardiac causes in patients with ischemic heart disease.

Though it was reported that the severity of COPD might affect in-hospital outocomes after PCI and CABG, we found that patients with COPD undergoing elective PCI and CABG had in-hospital morbidity and mortality rates comparable with those of controls after first elective PCI and CABG in this study. Previously it was demonstrated that post-CABG mortality was largely higher in patients with severe COPD receiving steroids than that of patients without COPD, however post-CABG mortality of patients with mild or moderate COPD was similar to that of patients without COPD[4, 5] . However the severity of COPD was not well examined because pulmonary function test was not recorded in our database, and so further study may be needed to investigate the relationship between severity of COPD and short- and long-term mortality in patients with ischemic heart disease.

This study has some limitations. The definition of COPD in our study was consistent with that in many other studies [1, 2, 9-11], and 240 patients with COPD were identified in our study, which accounted for 2.4% of total population. However, the definition of COPD might be slightly lenient because the results of pulmonary function tests were not recorded in our database. Because ventricular function was evaluated before PCI or CABG, substantial recovery of ventricular function may have occurred in

some patients with left ventricle dysfunction with a concomitant decrease in the risk of all-cause mortality and cardiac death. In this study, we found that after the first elective PCI and CABG, the in-hospital morbidity rates in patients with COPD and control were comparable. It has been reported that the severity of COPD might affect in-hospital outcomes after PCI and CABG [4, 5]; however, the severity of COPD was not adequately determined in our study because the results of pulmonary function tests were not recorded in our database. Moreover, we have no information regarding the adjunctive pharmacotherapy after discharge and the duration of some of these comorbidities; these parameters may influence long-term mortality and morbidity.

Acknowledgments

We are indebted to the clinical research coordinators for data collection and to Miss Yoko Kasakura for secretarial assistance.

References

1. Grover FL, Johnson RR, Marshall G, Hammermeister KE. Factors predictive of operative mortality among coronary artery bypass subsets. Ann Thorac Surg 1993;56(6):1296-306; discussion 1306-7.

2. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15(6):816-22; discussion 822-3.

3. Gardner SC, Grunwald GK, Rumsfeld JS, Mackenzie T, Gao D, Perlin JB, et al. Risk factors for intermediate-term survival after coronary artery bypass grafting. Ann Thorac Surg 2001;72(6):2033-7.

4. Samuels LE, Kaufman MS, Morris RJ, Promisloff R, Brockman SK. Coronary artery bypass grafting in patients with COPD. Chest 1998;113(4):878-82.

5. Michalopoulos A, Geroulanos S, Papadimitriou L, Papadakis E, Triantafillou K, Papadopoulos K, et al. Mild or moderate chronic obstructive pulmonary disease risk in elective coronary artery bypass grafting surgery. World J Surg 2001;25(12):1507-11.

6. Canver CC, Nichols RD, Kroncke GM. Influence of age-specific lung function

on survival after coronary bypass. Ann Thorac Surg 1998;66(1):144-7.

7. Clough RA, Leavitt BJ, Morton JR, Plume SK, Hernandez F, Nugent W, et al. The effect of comorbid illness on mortality outcomes in cardiac surgery. Arch Surg 2002;137(4):428-32; discussion 432-3.

8. Rosenthal GE, Vaughan Sarrazin M, Hannan EL. In-hospital mortality following coronary artery bypass graft surgery in Veterans Health Administration and private sector hospitals. Med Care 2003;41(4):522-35.

9. Medalion B, Katz MG, Cohen AJ, Hauptman E, Sasson L, Schachner A. Long-term beneficial effect of coronary artery bypass grafting in patients with COPD. Chest 2004;125(1):56-62.

10. van Domburg RT, Takkenberg JJ, van Herwerden LA, Venema AC, Bogers AJ. Short-term and 5-year outcome after primary isolated coronary artery bypass graft surgery: results of risk stratification in a bilocation center. Eur J Cardiothorac Surg 2002;21(4):733-40.

11. DeRose JJ, Jr., Toumpoulis IK, Balaram SK, Ioannidis JP, Belsley S, Ashton RC, Jr., et al. Preoperative prediction of long-term survival after coronary artery bypass grafting in patients with low left ventricular ejection fraction. J Thorac Cardiovasc Surg 2005;129(2):314-21.

12. Renzetti AD, Jr., McClement JH, Litt BD. The Veterans Administration cooperative study of pulmonary function. 3. Mortality in relation to respiratory function in chronic obstructive pulmonary disease. Aspen Emphysema Conf 1968;9:367-78.

13. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005-12.

14. Selvaraj CL, Gurm HS, Gupta R, Ellis SG, Bhatt DL. Chronic obstructive pulmonary disease as a predictor of mortality in patients undergoing percutaneous coronary intervention. Am J Cardiol 2005;96(6):756-9.

15. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. . Circulation 2008;118:S199-S209.

16. Collet D. Modelling Survival Data in Medical Resarch. 2nd Ed ed; 2003.

17. Behar S, Panosh A, Reicher-Reiss H, Zion M, Schlesinger Z, Goldbourt U. Prevalence and prognosis of chronic obstructive pulmonary disease among

5,839 consecutive patients with acute myocardial infarction. SPRINT Study Group. Am J Med 1992;93(6):637-41.

18. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc Am Thorac Soc 2005;2(1):8-11.

19. Fimognari FL, Scarlata S, Conte ME, Incalzi RA. Mechanisms of atherothrombosis in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2008;3(1):89-96.

20. Entwistle MD, Sommerville D, Tandon AP, Jones JG. Effect of hypoxaemia on the resting electrocardiogram (ECG) in patients with cardiac ischaemia. Ann Acad Med Singapore 1994;23(4):460-4.

21. Gill NP, Wright B, Reilly CS. Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. Br J Anaesth 1992;68(5):471-3.

22. Kleiger RE, Senior RM. Longterm electrocardiographic monitoring of ambulatory patients with chronic airway obstruction. Chest 1974;65(5):483-7.

23. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J 2003;21(6):1012-6.

24. Shih HT, Webb CR, Conway WA, Peterson E, Tilley B, Goldstein S. Frequency

and significance of cardiac arrhythmias in chronic obstructive lung disease. Chest 1988;94(1):44-8.

25. Fuso L, Incalzi RA, Pistelli R, Muzzolon R, Valente S, Pagliari G, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. Am J Med 1995;98(3):272-7.

26. Hudson LD, Kurt TL, Petty TL, Genton E. Arrhythmias associated with acute respiratory failure in patients with chronic airway obstruction. Chest 1973;63(5):661-5.

27. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease. A prospective study of 200 patients. N Engl J Med 1969;280(8):397-404.

28. Sarubbi B, Esposito V, Ducceschi V, Meoli I, Grella E, Santangelo L, et al. Effect of blood gas derangement on QTc dispersion in severe chronic obstructive pulmonary disease: evidence of an electropathy? Int J Cardiol 1997;58(3):287-92.

Figure legend

Unadjusted Kaplan-Meier Event-free Survival Curves for All-cause Mortality (Panel A), Cardiovascular death (Panel B), and Cardiac Death (Panel C).

COPD = chronic obstructive pulmonary disease

Appendices

Appendix A. List of participating centers and investigators

Centers	Investigators
Fukuroi Municipal Hospital	Katsuo Okazaki
Hamamatsu Rosai Hospital	Masaaki Takahashi Teiji Oda
Hikone Municipal Hospital	Shigeo Matsui Naohiro Ohashi
Himeji Medical Center	Eiichi Matsuyama Makoto Kadoya
Hyogo Prefectural Amagasaki Hospital	Yoshiki Takatsu Shinichi Nomoto Kazuaki Kataoka
Japanese Red Cross Society, Wakayama Medical Center	Hajime Kotoura Masaki Aota Akira Miura
Juntendo University Shizuoka Hospital	Satoru Suwa
Kagoshima University Medical and Dental Hospital	Chuwa Tei

	Ryuzo Sakata
	Shuichi Hamasaki
	Hiroyuki Yamamoto
Kansai Denryoku Hospital	Takeshi Aoyama
	Takahiro Sakurai
Kishiwada City Hospital	Mitsuo Matsuda
	Masahiko Onoe
	Yuzo Takeuchi
Kitano Hospital	Ryuji Nohara
	Kimisato Nakano
Kobe City Medical Center General Hospital	Shigefumi Morioka
	Yukikatsu Okada
	Kenichi Shiratori
	Nasu Michihiro
Kokura Memorial Hospital	Masakiyo Nobuyoshi

	Hitoshi Okabayashi
	Hitoshi Yasumoto
	Jyota Nakano
Koto Memorial Hospital	Tomoyuki Murakami
	Katsuya Ishida
Kumamoto University Hospital	Hisao Ogawa
	Michio Kawasuji
	Seigo Sugiyama
	Shoichiro Hagiwara
Kurashiki Central Hospital	Kazuaki Mitsudo
	Tatsuhiko Komiya
	Kazushige Kadota
Kyoto University Hospital	Takeshi Kimura
	Masashi Komeda
Maizuru Kyosai Hospital	Ryozo Tatami
	Teruaki Ushijima
Mitsubishi Kyoto Hospital	Akira Yoshida

	Hiroyuki Nakajima
	Shinji Miki
Nara Hospital, Kinki University School of Medicine	Ryuichi Hattori
	Noboru Nishiwaki
	Manabu Shirotani
Nishi-Kobe Medical Center	Hiroshi Kato
	Hiroshi Eizawa
Osaka Red Cross Hospital	Masaru Tanaka
	Kazuaki Minami
Shiga University of Medical Science Hospital	Minoru Horie
	Tohru Asai
	Hiroyuki Takashima
	Ryuji Higashita
Shimabara Hospital	Mamoru Takahashi
	Takafumi Tahata
	Yoshiki Matoba
Shimada Municipal Hospital	Kiyoshi Doyama

	Makoto Araki
Shizuoka City Shizuoka Hospital	Akinori Takizawa
	Mitsuomi Shimamoto
	Fumio Yamazaki
Shizuoka General Hospital	Osamu Doi
	Hirofumi Kambara
	Katsuhiko Matsuda
	Satoshi Kaburagi
	Masafumi Nara
Takanohara Central Hospital	Masaki Kawanami
Tenri Hospital	Takashi Konishi
	Kazunobu Nishimura
	Seiji Ootani
	Takaaki Sugita

Appendix B. List of clinical research coordinators

Kumiko Kitagawa, Hiromi Yoshida, Misato Yamauchi, Asuka Saeki, Chikako Hibi, Emi Takinami, Izumi Miki, Miya Hanazawa, Naoko Okamoto, Sachiko Maeda, Saeko Minematsu, Saori Tezuka, Yuki Sato, Yumika Fujino, Hitomi Sasae, Rei Fujita, Ayu Motofusa, Takami Hiraoka, Ayumi Yamamoto, Miho Hayashikawa, and Yoko Fujiki

A.J.S. Coats , MD

Editor-in-Chief: INTERNATIONAL JOURNAL OF CARDIOLOGY

October, 2008

Dear Professor A.J.S. Coats:

Please find our manuscript entitled “Chronic Obstructive Pulmonary Disease—an Independent Risk Factor for Long-term Cardiac and Cardiovascular Mortality in Patients with Ischemic Heart Disease” by Kei Nishiyama et al., which we would like to submit for publication as original research papers. Chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD) share smoking as a risk factor, so these two diseases often coexist. Previous studies have shown patients with COPD have a significantly higher risk of long-term all-cause mortality after having PCI and CABG. This study also demonstrated patients with COPD also have higher long-term mortality rates than those without COPD after first elective PCI and CABG. The question of how having COPD affect long-term mortality and morbidity in patients with ischemic heart disease remains unsettled. To our knowledge, this study is the first

report showing patients with COPD have a significantly higher risk of cardiac death and cardiovascular death after having PCI and CABG.

The manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language. All authors have read and approved the manuscript. No conflict of interests exists in any of the authors in this study.

Your kind consideration would be greatly appreciated.

Yours sincerely,

Kei Nishiyama, MD

Department of Cardiovascular Medicine,

Kyoto University Graduate School of Medicine,

54 Shogoinkawahara-cho, Sakyo-ku,

Kyoto, 606-8507, Japan

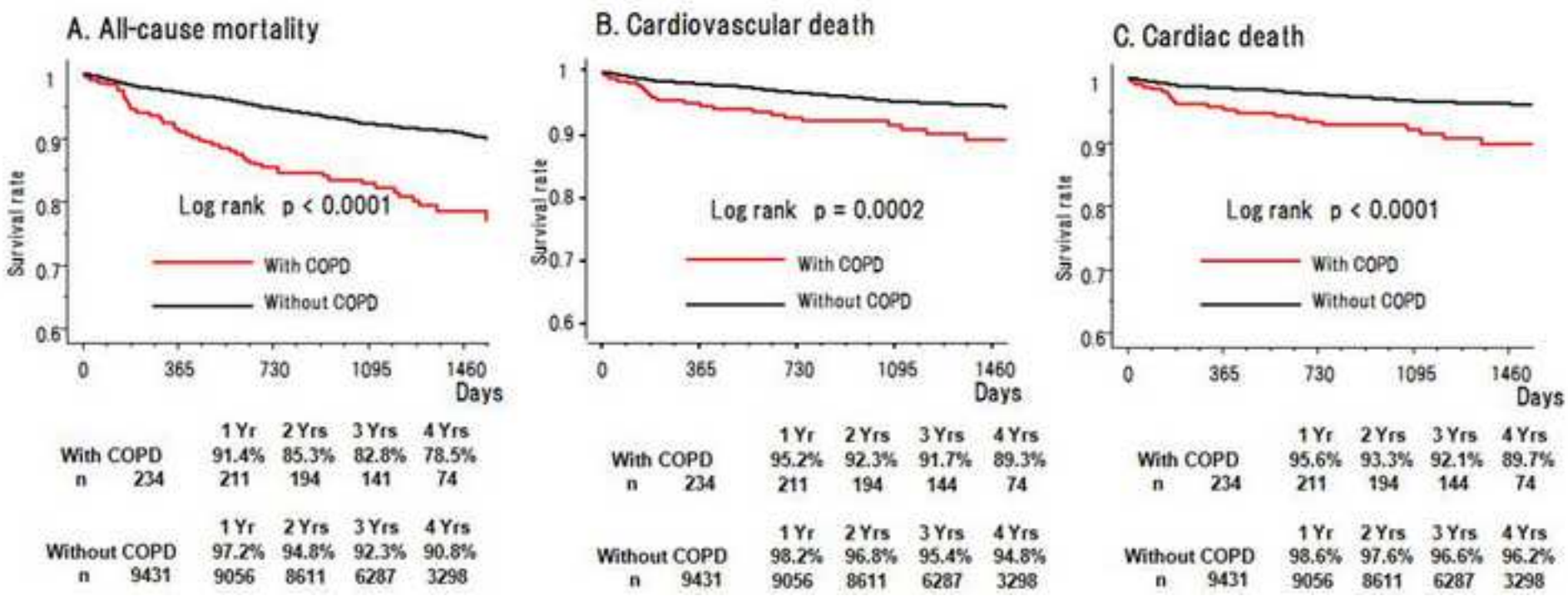
(Tel) 81-7-5751-3198

(Fax) 81-7-5751-3299

(E-mail) keinishi@kuhp.kyoto-u.ac.jp

Figure 1

Click here to download high resolution image



		1 Yr	2 Yrs	3 Yrs	4 Yrs
With COPD		91.4%	85.3%	82.8%	78.5%
n	234	211	194	141	74
Without COPD		97.2%	94.8%	92.3%	90.8%
n	9431	9056	8611	6287	3298

		1 Yr	2 Yrs	3 Yrs	4 Yrs
With COPD		95.2%	92.3%	91.7%	89.3%
n	234	211	194	144	74
Without COPD		98.2%	96.8%	95.4%	94.8%
n	9431	9056	8611	6287	3298

		1 Yr	2 Yrs	3 Yrs	4 Yrs
With COPD		95.6%	93.3%	92.1%	89.7%
n	234	211	194	144	74
Without COPD		98.6%	97.6%	96.6%	96.2%
n	9431	9056	8611	6287	3298

Table 1. Patient and Disease Characteristics

	COPD				p-value
	Yes (n=240)		No (n=9632)		
	n	%	n	%	
Having PCI	166	69.2%	6709	69.7%	0.8715
Female gender	42	17.5%	2855	29.6%	<0.0001
Emergency procedure	12	5.0%	532	5.4%	0.7212
Proir myocardial infarction	71	29.7%	2476	25.7%	0.1730
Congestive heart failure	51	21.3%	1216	12.7%	0.0003
Stroke	54	22.5%	1587	16.5%	0.0177
Peripheral artery disease	38	15.8%	1101	11.4%	0.0447
Chronic atrial fibrillation	20	8.3%	653	6.8%	0.5787
Malignancy	23	9.6%	680	7.1%	0.1523
Hypertension	150	62.5%	6657	69.2%	0.0303
Diabetes without insulin therapy	59	24.6%	2957	30.7%	0.0491
Diabetes with insulin therapy	17	7.1%	223	8.3%	0.4770
Dialysis	5	2.1%	402	4.2%	0.0769
Chronc kidney disease	137	58.8%	3775	40.4%	<0.0001
Anemia	77	32.5%	2458	26.1%	0.0320
Current smoker status	105	43.8%	3375	35.7%	0.5340
Left ventricular dysfunction	31	14.2%	708	8.1%	0.0031
Chronic total occulusion of coronary artery	80	33.3%	2941	30.5%	0.3759
Proximal left anterior descending coronary artery disease	171	71.3%	6916	71.8%	0.8453
Left main coronary artery disease	22	9.2%	933	9.7%	0.7851
Triple vessel disease	80	33.3%	3123	31.6%	0.7691

	COPD		p-value
	Yes (n=240)	No (n=9632)	
Age	72.7 ± 7.95	67.2 ± 10.00	<0.0001
Body mass index	21.7 ± 3.7	23.7 ± 3.2	<0.0001

COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention.

Table 3. Cox Proportional-Hazards Model for All-cause Mortality and Cardiac Death

	Not-adjusted			*Adujusted*		
Clinical Outcomes	HR	95% CI	p-value	HR	95% CI	p-value
All-Cause mortality (n=906)	1.60	1.38-1.83	<0.0001	1.36	1.16-1.57	0.0003
Cardiac death (n=376)	1.65	1.31-2.02	0.0002	1.45	1.14-1.81	0.004

HR = hazard ratio; CI = confidential index.

Table 2. In-hospital Outcomes

	COPD		
	Yes	No	p-value
Clinical Outcomes	(n=240)	(n=9632)	
In-hospital death	3 1.3%	118 1.2%	0.9724
In-hospital QMI	2 0.8%	91 0.9%	0.8572
MACE	7 2.9%	235 2.4%	0.6464
Hospitalization (days)	22.6±29.6	18.1±21.7	0.0034

COPD = chronic obstructive pulmonary disease; QMI = Q-wa
myocardial infarction; MACE = major adverse cardiac event.